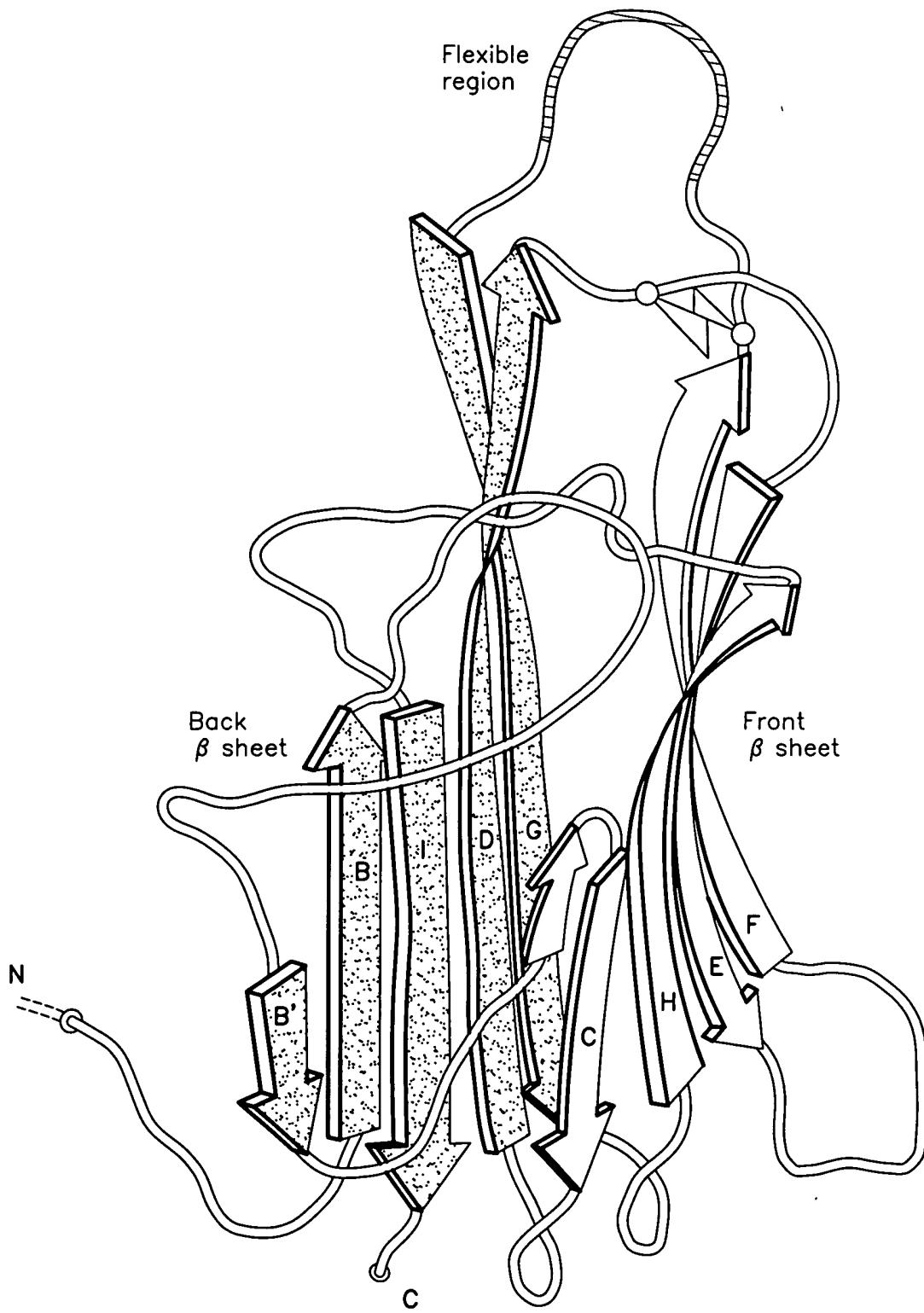




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# FIG. 1a

Crystal Structure of TNF







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FIG. 1c

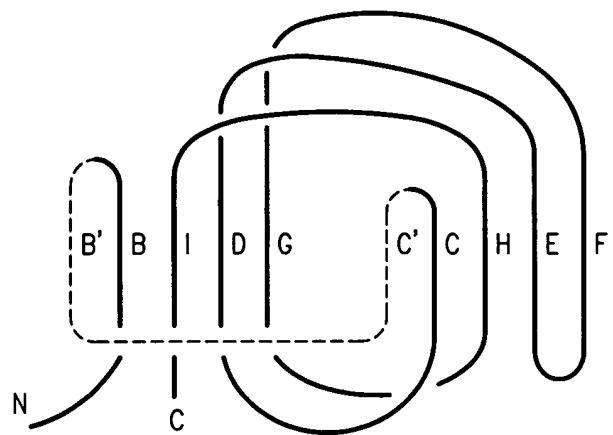
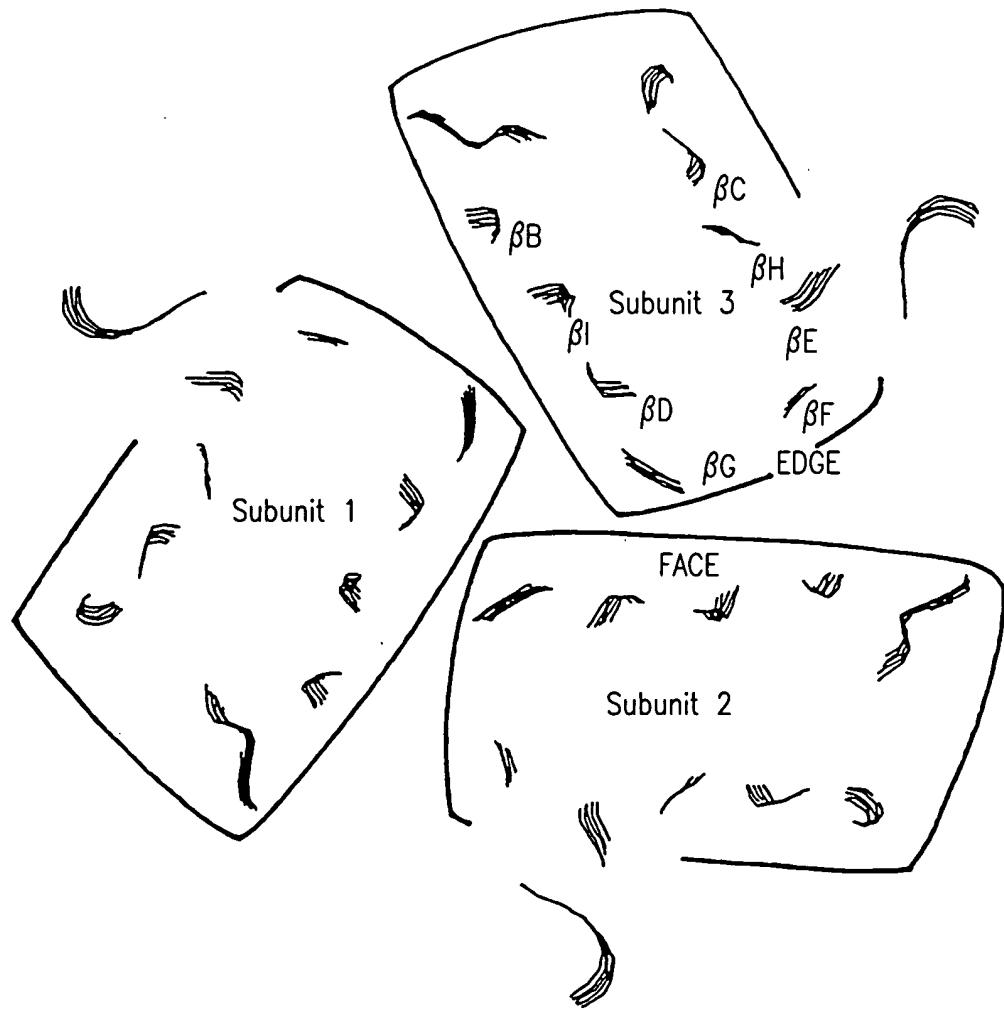


FIG. 2





## FIG. 3a

1 cacaccctga caagctgcc a ggcaggctc cttcctctca catactgacc  
51 cacggctcca ccctctctcc cctggaaagg acaccatgag cactgaaagc  
101 atgatccggg acgtggagct ggccgaggag gcgcctccca agaagacagg  
151 ggggccccag ggctccaggc ggtgcttgtt cctcagcctc ttctccttcc  
201 ttagatcggtgc aggccgccacc acgctcttct gcctgctgca ctttggagtg  
251 atcggccccc agagggaaaga gtcccccagg gacctctctc taatcagccc  
301 tctggcccaag gcagtcatag catcttctcg aaccccgagt gacaagcctg  
351 tagcccatgt ttagcaaaac cctcaagctg aggggcagct ccagtggctg  
401 aaccgcggg ccaatgcct cctggccaaat ggcgtggagc tgagagataa  
451 ccagctggtg gtgcctatcag agggcctgtt cctcatctac tcccaagggtcc  
501 tcttcaaggg ccaaggctgc ccctccaccc atgtgctcct caccacacc  
551 atcagccgca tcgcccgtctc ctaccagacc aaggtcaacc tcctctctgc  
601 catcaagagc ccctggcaga gggagacccc agagggggct gaggccaagc  
651 cctggatgtga gcccattat ctggggagggg tcttccagct ggagaagggt  
701 gaccgactca ggcgtgagat caatcgccc gactatctcg acttgcgcga  
751 gtctgggcag gtctactttg ggcatttcgc cctgtgagga ggacgaacat  
801 ccaacccctcc caaacgcctc ccctggccca atccctttat taccggctcc  
851 ttcagacacc ctcaacctct tctggctcaa aaagagaatt gggggcttag  
901 ggtcggaacc caagcttaga actttaagca acaagaccac cacttcgaaa  
951 cctgggattc aggaatgtgt ggcctgcaca gtgaagtgt ggcaaccact  
1001 aagaattcaa actggggct ccagaactca ctggggccta cagcttgat  
1051 ccctgacatc tggaaatctgg agaccaggaa gccttgggtt ctggccagaa  
1001 tgctgcagga ctggagaaga cctcacctag aaattgacac aagtggacct  
1151 taggccttcc tctctccaga tggggccaga ctcccttgag acacggagcc  
1201 cagccctccc catggagcca gctccctcta ttatgtttt cacttgcgt  
1251 tatttattat ttatattat tttatattt tacagatgaa tgtatattt  
1301 tgggagaccg gggatccctg ggggacccaa tggggatggact gccttggctc  
1351 agacatgttt tccgtaaaaa cggaggctga acaataggt gttcccatgt  
1401 agccccctgg cctctgtgcc ttctttgtat tatgtttttt aaaaatattat  
1451 ctgatatagt tggatccaaatc atgctgattt ggtgaccaac tgtcactcat  
1501 tgctgaggcc tctgctcccc agggagttgt gtctgtatc ggctactat  
1551 tcagtggcga gaaataaagg ttgcttagga aagaa



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## FIG. 3b

Amino acid sequence for human TNF $\alpha$ <sup>8</sup>

Accession code: Swissprot P01375

-76	MSTESMIRDV	ELAEEALPKK	TGGPQGSRRC	LFLSLFSFLI	VAGATTLFCL
-26	LHFGVIGPQR	EEFPRDLSLI	SPLAQA		
1	VRSSSRTPSD	KPVAHWANP	QAEGQLQWLN	RRANALLANG	VELRDNQLW
51	PSEGLYLIYS	QVLFKGQGCP	STHVLLLHTI	SRIAVSYQTK	VNLLSAIKSP
101	CQRETPEGAE	AKPWYEPIYL	GGVFQLEKGD	RLSAEINRPD	YLDFAESGQV
151	YFGIIAL				

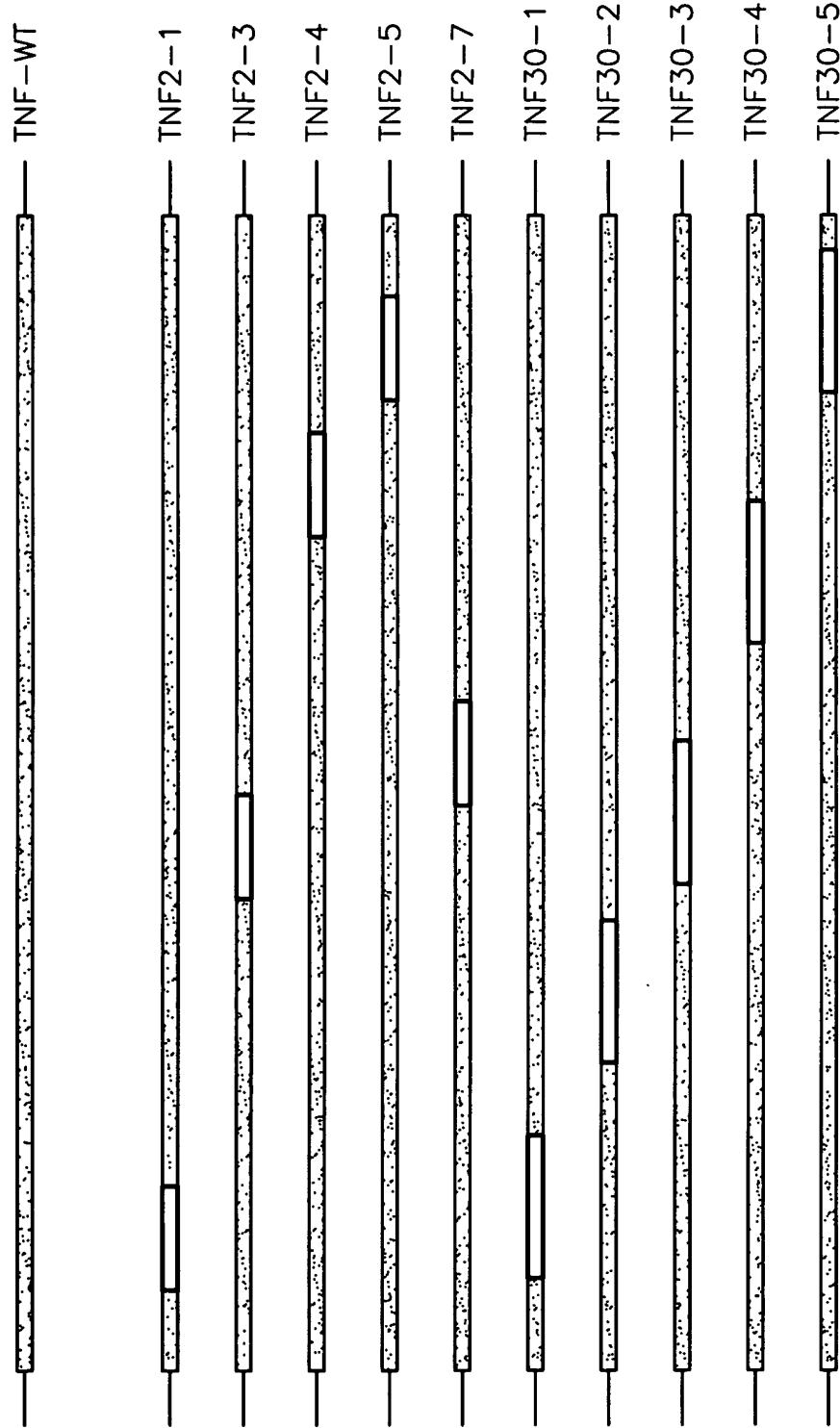
Conflicting sequence F->S at position -14. Disulphide bond between Cys69-101. Signal anchor sequence -41 to -21 (underlined). Myristylation on Lys-58/-57.



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## FIG. 4a

Location of inserted epitopes





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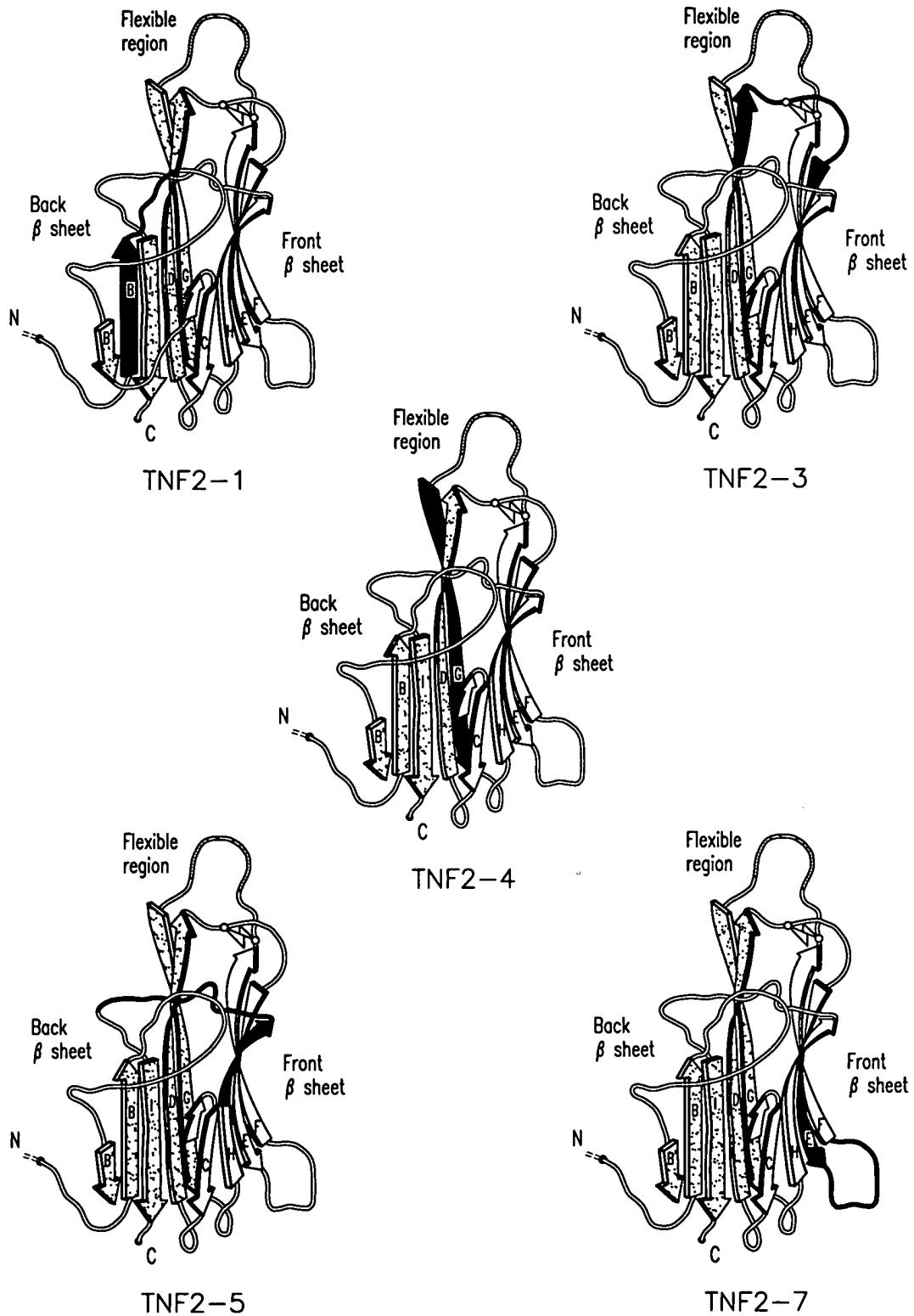
## FIG. 4b

#	1	11	21	31	41	51	61	71
WT	VRSSSSRTPSD	KPVAHVWANP	QAEGQLQWLN	RRANALLANG	VELRDNQWLW	PSEGLYIYS	QVLFKGQQCP	STHVLLLHTI
2-1	-----Q	YIKANSKFIG	ITEL-----	-----	-----	-----	-----	-----QYIKANSKFIGITEL-----
2-3	-----	-----	-----	-----	-----	-----	-----	-----
2-4	-----	-----	-----	-----	-----	-----	-----	-----
2-5	-----	-----	-----	-----	-----	-----	-----	-----
2-7	-----	-----	-----	-----	-----	-----	-----	-----QYIKA
30-1	-----F	NNFTVSFWLRL	VPKVSAASHLE	-----	-----	-----	-----	-----
30-2	-----	-----	-----	-----F	NNFTVSFWLRL	VPKVSAASHLE	-----	-----
30-3	-----	-----	-----	-----	-----	-----	FNNFTVS	FWLVRPKVSA
30-4	-----	-----	-----	-----	-----	-----	-----	-----
30-5	-----	-----	-----	-----	-----	-----	-----	-----
WT	SRIAVSYQTK	VNLLSAIKSP	CQRETPEGAE	AKPWYEPYL	GGVFQLEKGD	RLSAEINRPD	YLDFAESGQV	YFGIIAL
2-1	-----	-----	-----	-----	-----	-----	-----	-----
2-3	-----	-----	-----	-----	-----	-----	-----	-----
2-4	-----	-----	-----	-----QYIKANS	KFIGITEL-----	-----	-----	-----
2-5	-----	-----	-----	-----	-----	-----QYKANSK	-----	-----IGITEL-----
2-7	NSKFIGITEL	-----	-----	-----	-----	-----	-----	-----
30-1	-----	-----	-----	-----	-----	-----	-----	-----
30-2	-----	-----	-----	-----	-----	-----	-----	-----
30-3	SHLE-----	-----	-----	-----	-----	-----	-----	-----
30-4	-----	-----	-----FNNFT	VSFWLVRPKV	SASHLE-----	-----	-----	-----
30-5	-----	-----	-----	-----	-----	-----FNNFTVSFW	LRVPKVSASH	LE-----



## FIG. 5a

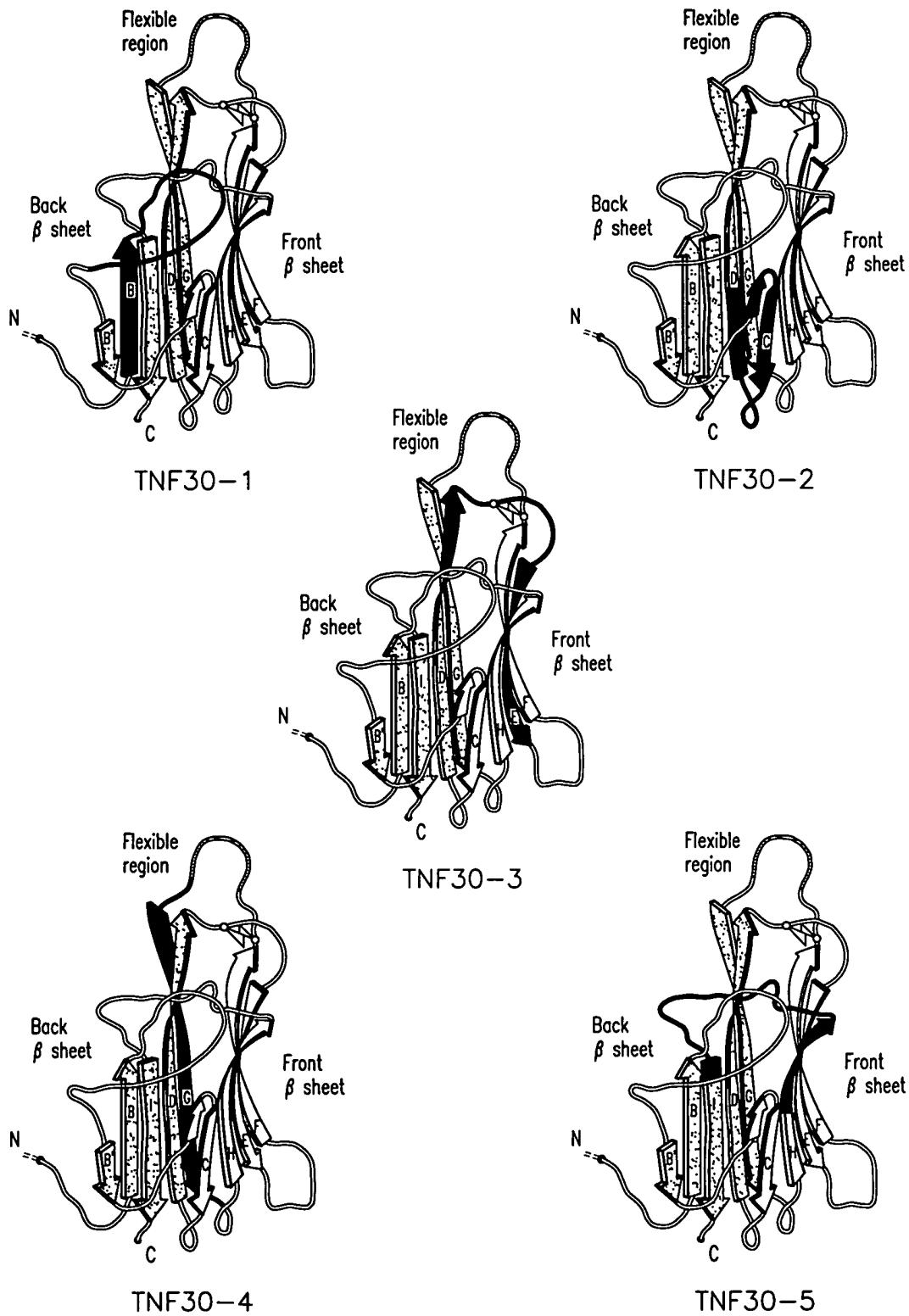
### TNF $\alpha$ analogs with the P30 epitope inserted





## FIG. 5b

### TNF $\alpha$ analogs with the P30 epitope inserted



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FIG. 6

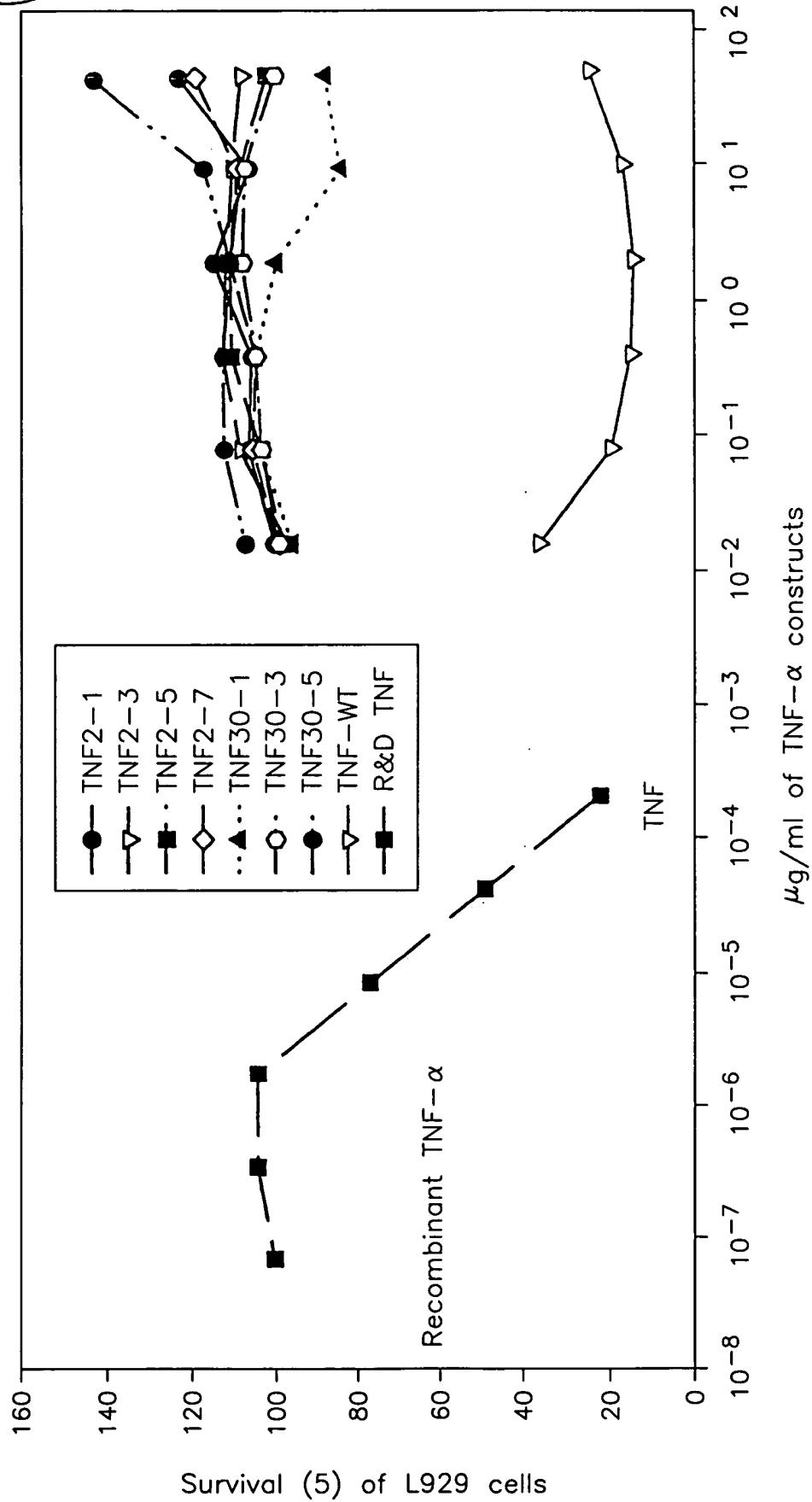
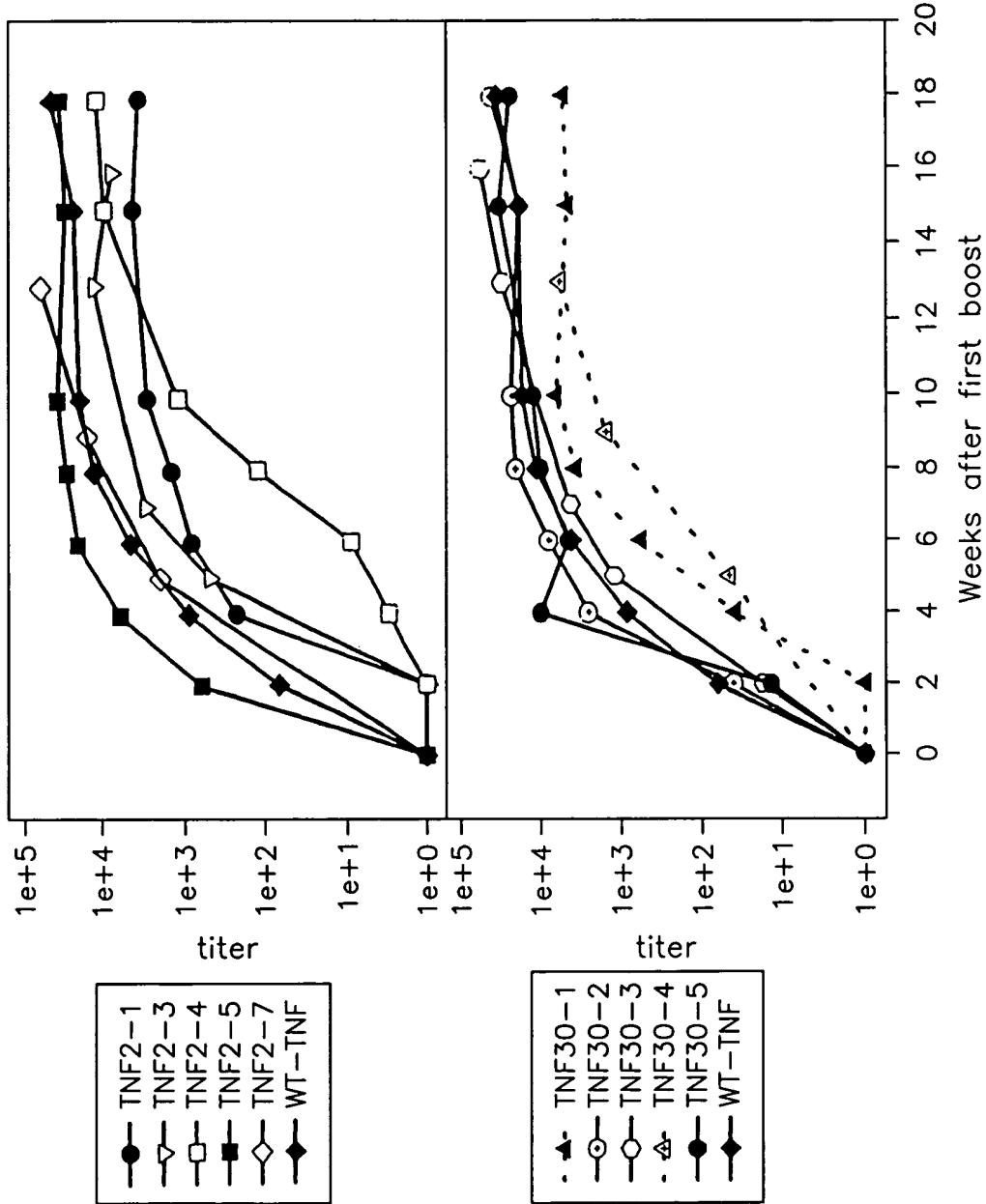




FIG. 7

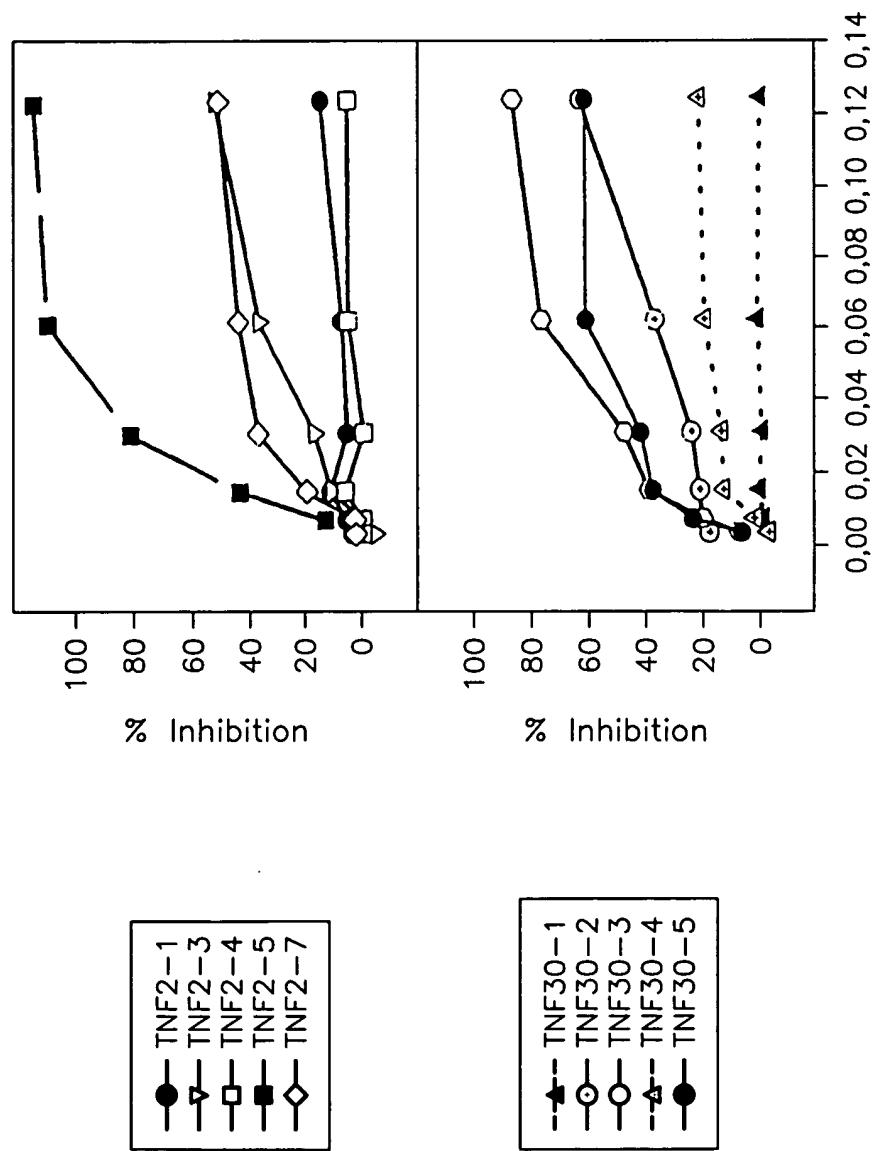
The anti human TNF antibody response in rabbits





**FIG. 8**

The ability of P2/P30 modified human TNF $\alpha$  molecules to induce neutralizing antibodies as measured in the L929 cell assay





**FIG. 9**

The ability of P2/P30 modified human TNF $\alpha$  molecules to induce neutralizing antibodies as measured in the receptor assay

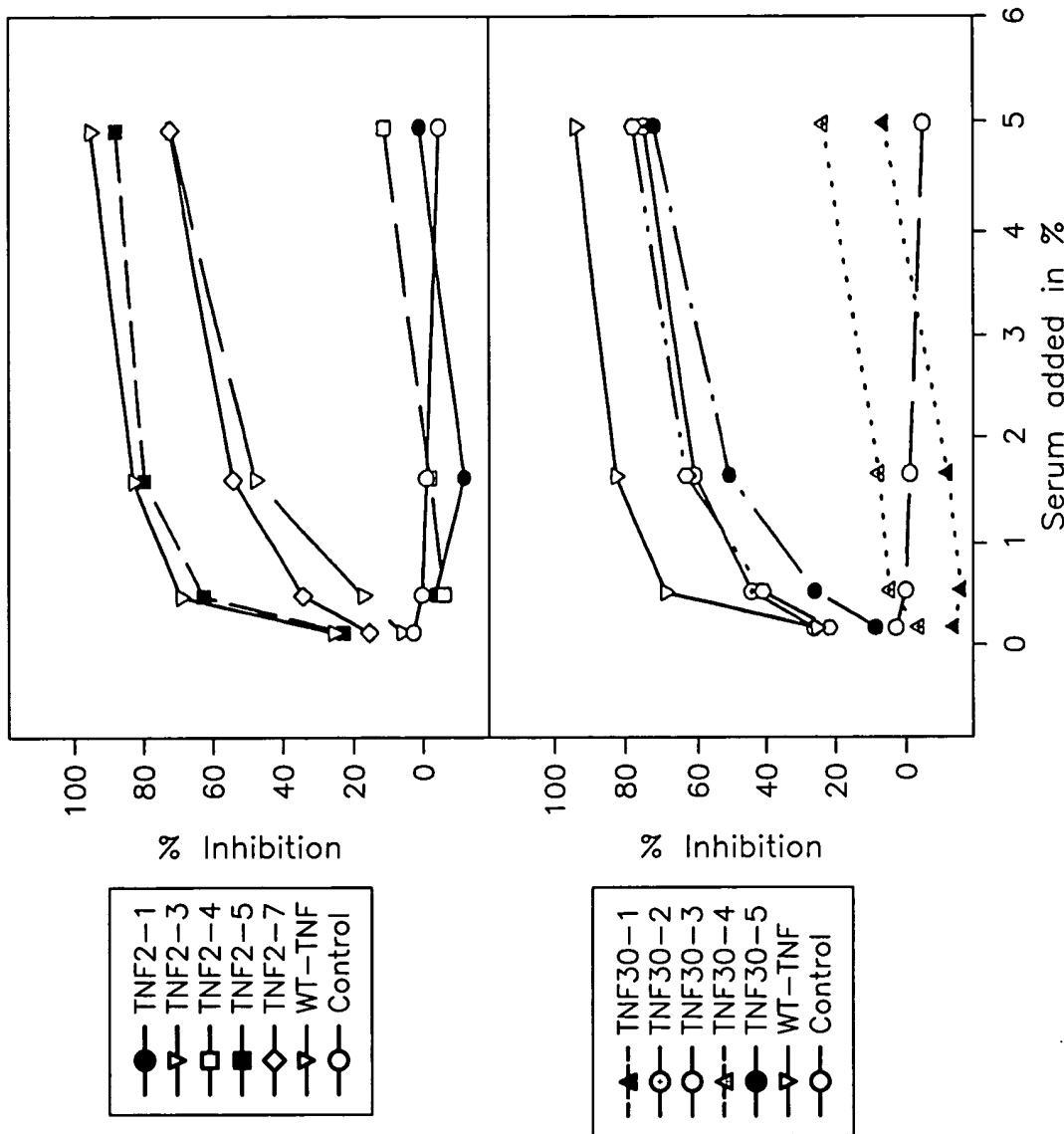




FIG. 10

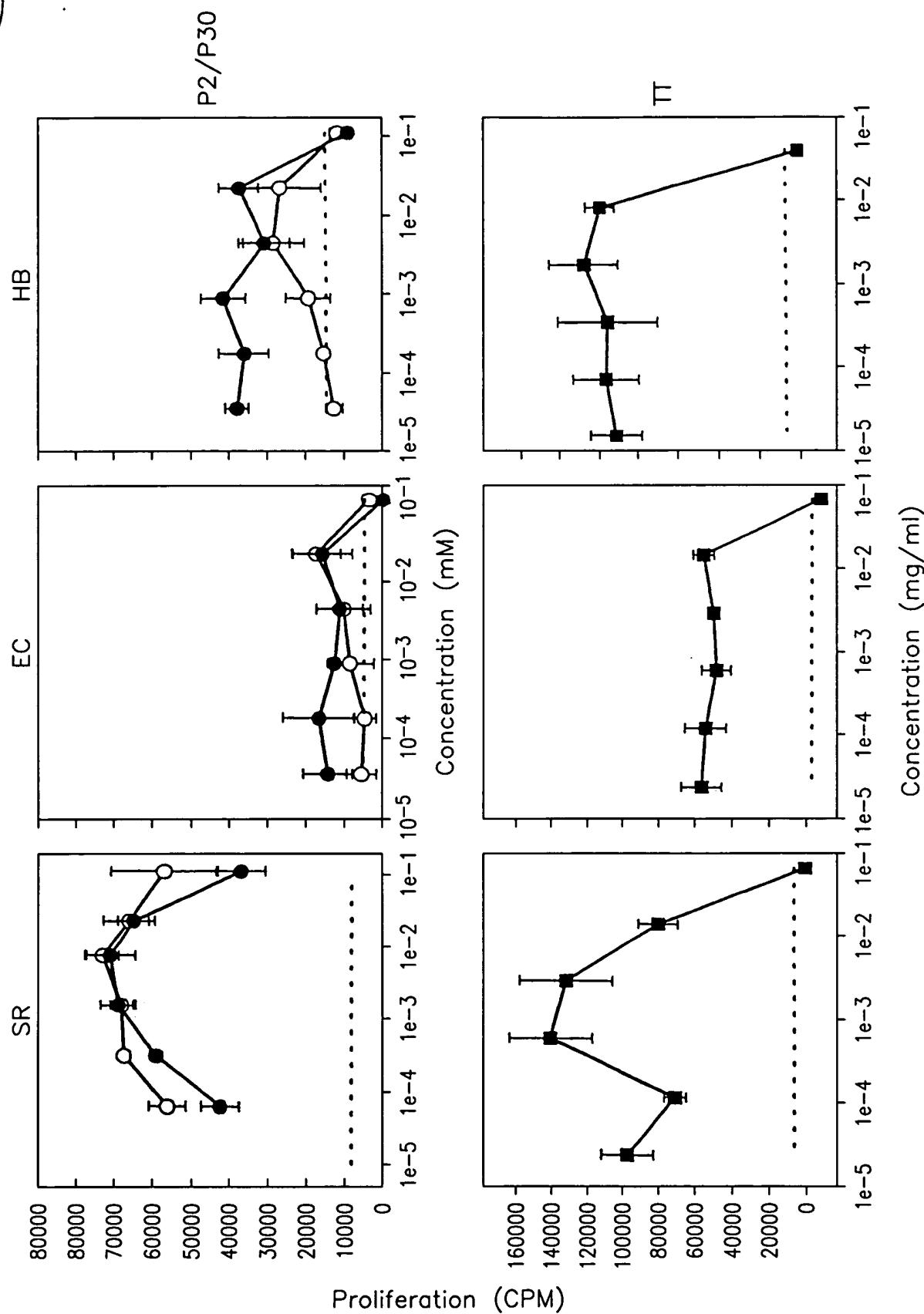




FIG.

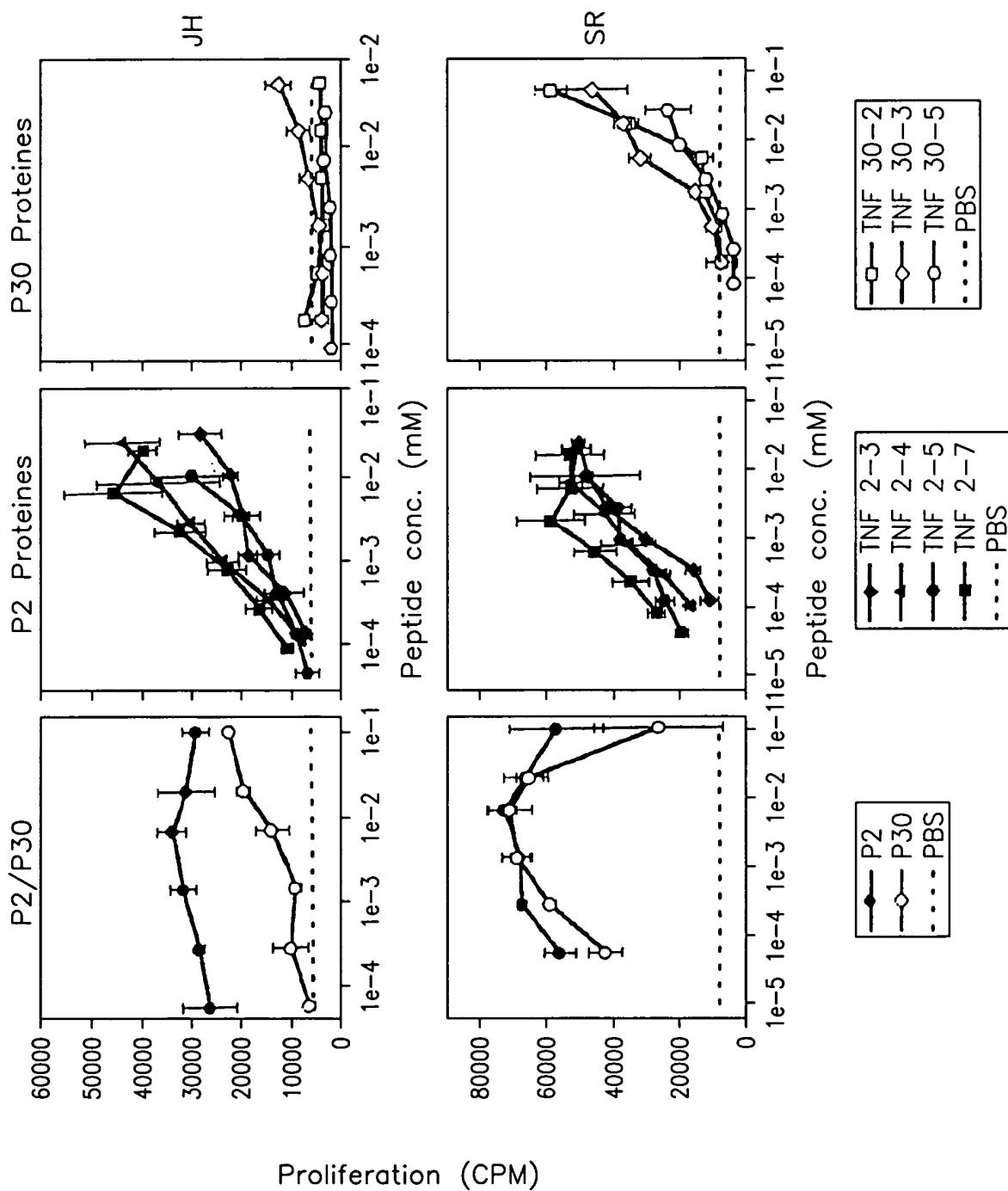
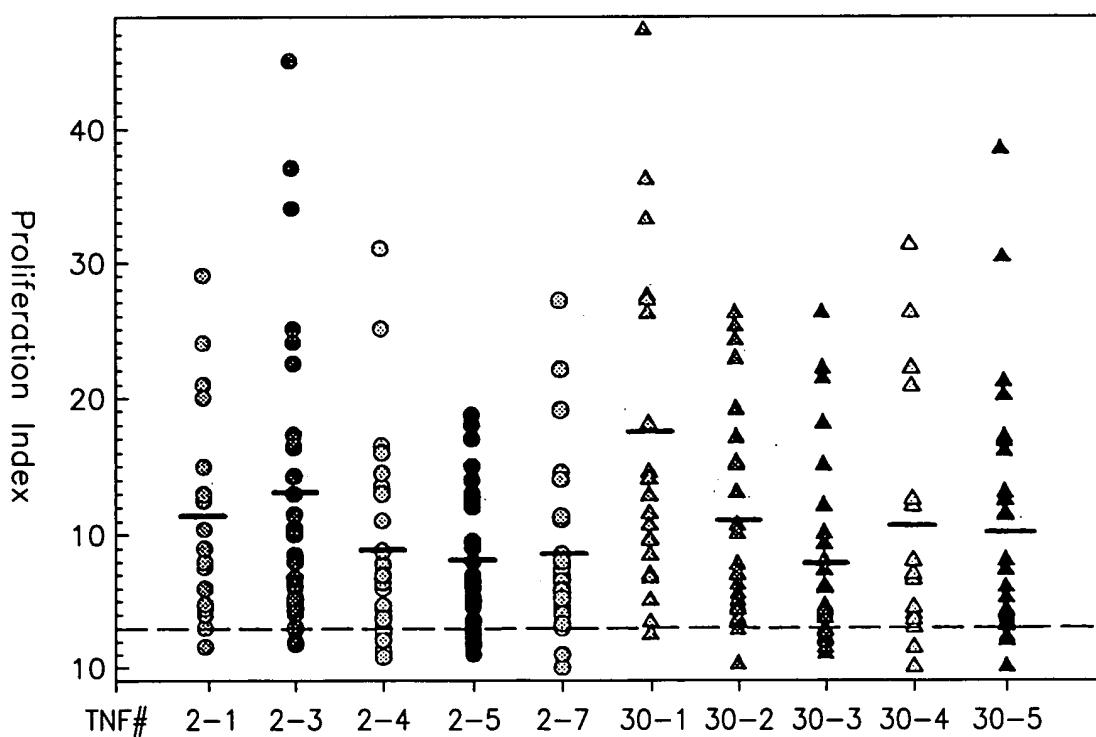




FIG. 12

PBMC Assays

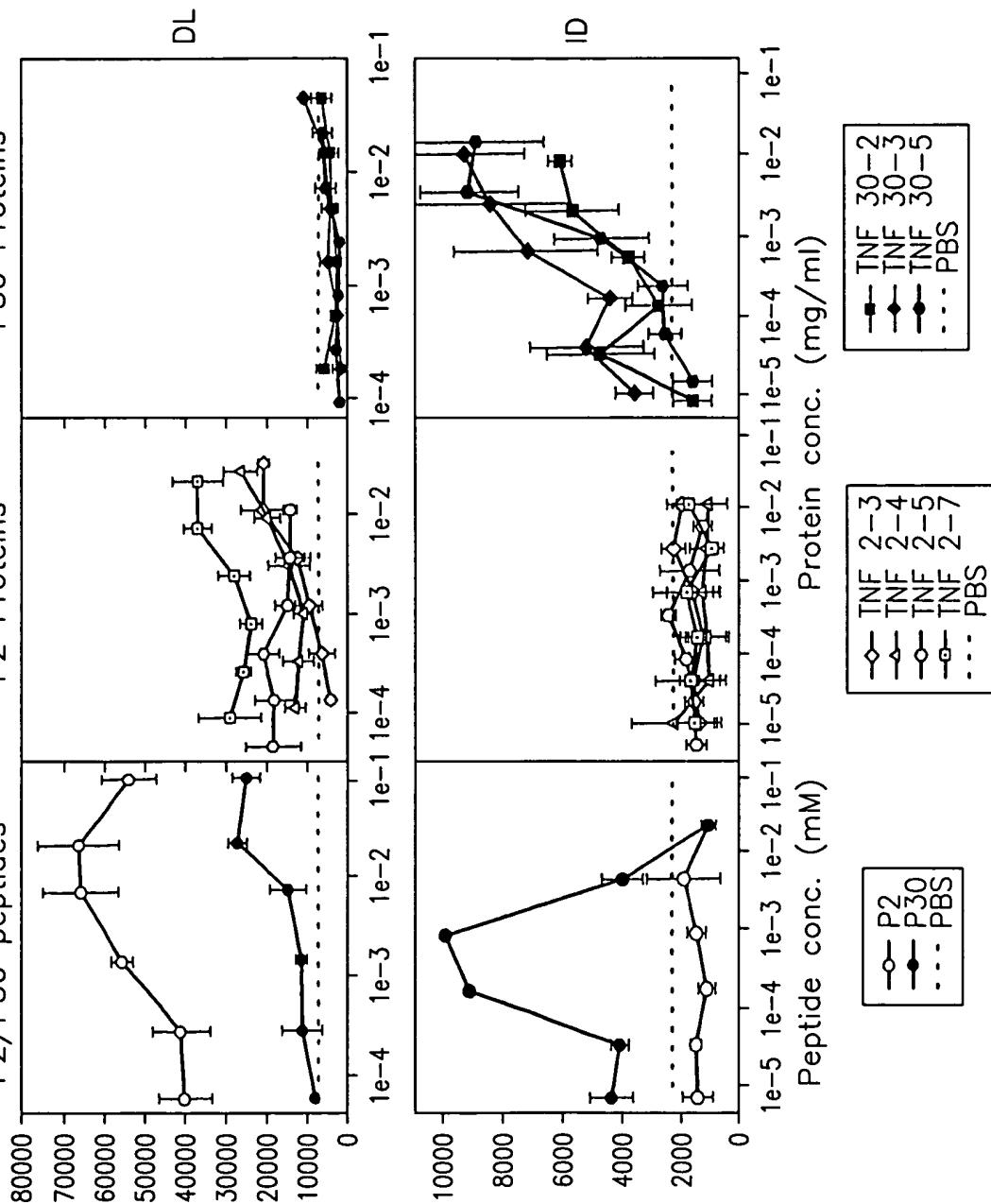




## FIG. 13

The PBMC response against P2 and P30 modified TNF proteins in P2 and P30 specific responders, respectively

P30 Proteins





**FIG. 14**

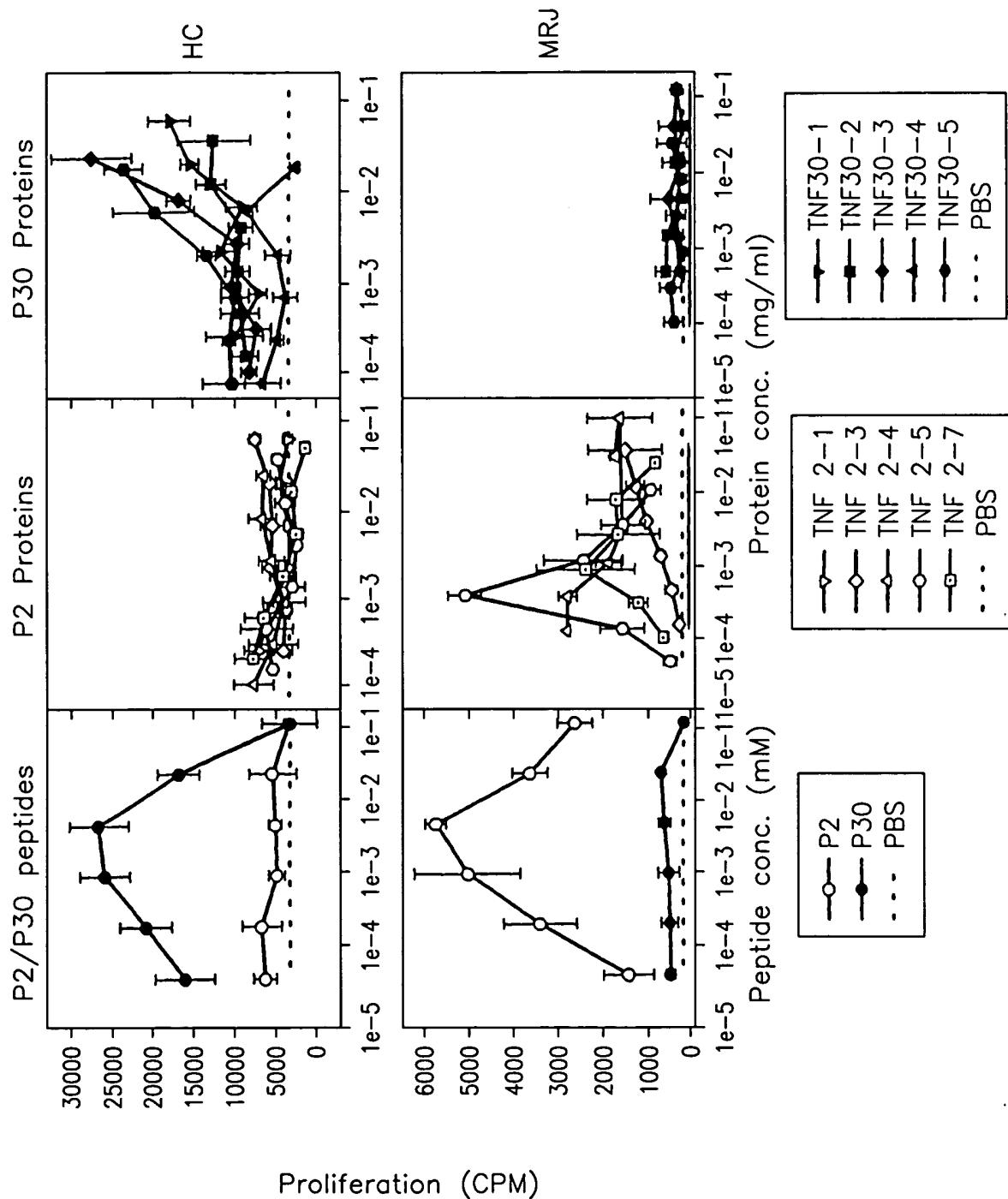
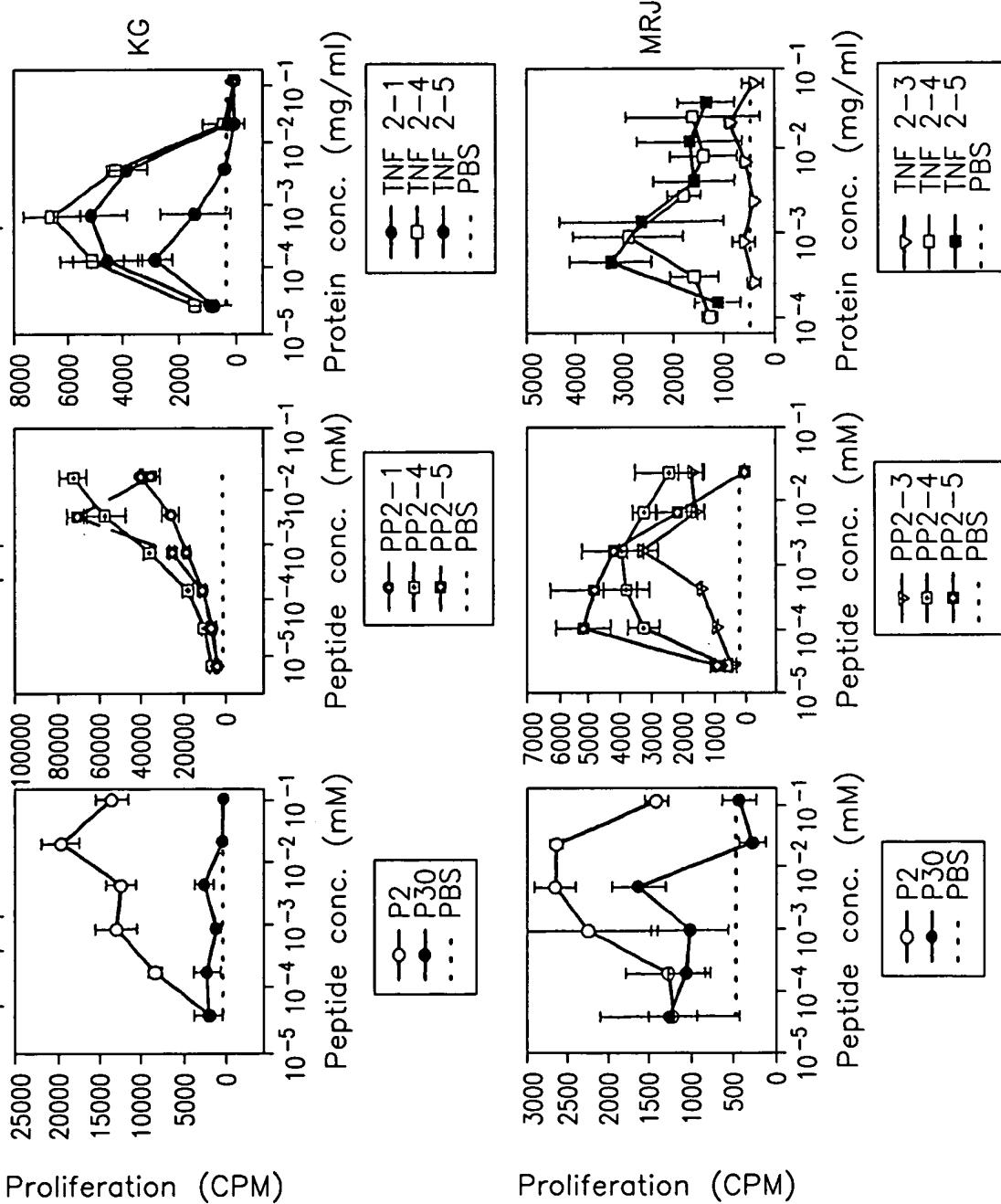




FIG. 15

The influence of flanking amino acids on the T cell recognition of P2 and P30 P2 peptides





## FIG. 16

Mutation Strategy

